WHO/CONRAD Technical Consultation on Nonoxynol-9

World Health Organization, Geneva, 9 – 10 October 2001

Summary Report

LIST OF ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
DHS	Demographic and Health Surveys
GPA	Global Programme on AIDS (WHO)
HIV	Human Immunodeficiency Virus
IPPF	International Planned Parenthood Federation
N-9	Nonoxynol-9
NSFG	National Survey of Family Growth
OTC	Over-the-counter
RHR	Department of Reproductive Health and Research (WHO)
RR	Relative Risk
STI	Sexually Transmitted Infection
UNAIDS	Joint United Nations Program on HIV/AIDS
UNFPA	United Nations Population Fund
USA	United States of America
USAID	United States Agency for International Development
VCF	Vaginal Contraceptive Film
WHO	World Health Organization

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Acknowledgement

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Introduction

An effective, easy to use vaginal microbicide would provide women with a method under their own control with which to protect themselves against infection with the human immunodeficiency virus (HIV). While many novel compounds are currently being developed and tested, it will be many years before a new product can be fully evaluated and distributed to users. The spermicide Nonoxynol-9 (N-9) has been widely available as a contraceptive for many years and has been shown to be effective against HIV in laboratory studies. If it also provided effective protection against HIV in clinical studies, N-9 could be made rapidly available to women who require protection. The World Health Organization Global Programme on AIDS (GPA) and the Joint United Nations Program on HIV/AIDS (UNAIDS) sponsored a clinical trial of a gel containing N-9 to assess its effectiveness in protecting against HIV. Preliminary results from the study were presented in July 2000 at the 13th International AIDS Conference in Durban, South Africa, and showed, contrary to expectation, that the HIV incidence was higher in women using N-9 than in women using a comparison product. While a disappointment with regard to the rapid deployment of an effective microbicide, these results also raised questions about the safety of N-9 when used for its main indication, protection against unwanted pregnancy.

After presentation of the preliminary results from the study in July 2000, the World Health Organization (WHO) was approached to provide an assessment of the scientific information regarding the safety and effectiveness of N-9 when used for family planning purposes. This summary should permit Member States to assess the risks and benefits of N-9 use among women in their country who may be at risk of HIV infection from inadequately protected sexual activity. Accordingly, the WHO Department of Reproductive Health and Research (RHR) convened a Technical Consultation in October 2001, in partnership with the CONRAD Program, Arlington, VA, USA, to review the available evidence and provide advice to member states on the use of N-9. The Consultation included experts from developed and developing countries with experience in product development, safety assessment, and public health and representatives from collaborating agencies (Annex). Reviews of key issues were commissioned prior to the meeting and are summarised in this report. The meeting also considered the submitted manuscripts from recently completed studies directly relevant to the safety and effectiveness of N-9.

This report summarises the evidence presented to the meeting on the safety of N-9 and its effectiveness for protection against pregnancy, sexually transmitted infections (STIs) and HIV. The meeting concluded with recommendations on the use of N-9 and identified key areas of uncertainty where more research was urgently required.

Review of evidence

Use of Nonoxynol-9 containing products in developed and developing countries

A background paper on the use of N-9 containing products in developed and developing countries had been prepared by Kirsten Vogelsong (WHO) and Jeff Spieler (USAID) on the basis of marketing information from the principal manufacturers, national survey data from the United States of America (USA), the Demographic and Health Surveys (DHS), and information on product procurement and distribution from the three principal public sector

distributors – USAID, the United Nations Population Fund (UNFPA) and the International Planned Parenthood Federation (IPPF).

The authors identified a total of 18 spermicidal products containing N-9 in different formulations (gels, creams, vaginal suppositories and film) each containing between 50 and 150 mg of N-9. In addition, spermicides containing other active ingredients, such as octoxynol-9, benzalkonium chloride and menfegol, are also distributed in developed and developing countries. The private sector sales and market share of different types of spermicide in developing countries were difficult to establish. Public sector sales through donors revealed very uneven distribution of spermicides and large variations year to year in procurement.

According to DHS data, fewer than 1% of women in Asia reported ever using spermicides. These methods are more commonly used in Latin America than in other parts of the world. While between 5% and 10% of women reported ever using spermicides, current use was less than 1%. The highest reported use was Trinidad and Tobago where 16.6% of women reported ever use and 3.5% current use. Reported use by unmarried women and women under age 25 years was higher than among married women.

In the United States, based on data from the National Survey of Family Growth (NSFG) in 1995, 4.6% of women who used any contraceptive method used spermicide (alone or with a barrier method). It is not known what proportion of spermicide use refers to different formulations, but all spermicides in the USA contain N-9. The majority of the reported use is in combination with a physical barrier method, such as the diaphragm or cervical cap. Current use of these products fell by more than 50% since the earlier round of the NSFG conducted in 1988 where 10.6% of respondents reported current use. The trend of decreasing spermicide use in the USA has also been seen in decreasing private sector sales in other parts of the world. Comparable data on trends in the use of N-9-lubricated condoms were not available. NSFG data did not show a decreasing trend in use with increasing age, nor preferential use among unmarried women.

The characteristics of spermicides make them particularly attractive to unmarried women and young people. They are available over-the-counter (OTC), in addition to traditional family planning service delivery points, which distribute provider-dependent methods. Spermicides thus represent one of the few options to reduce the risk of unwanted pregnancy for young unmarried women who have poor access to provider-dependent methods.

Although the analysis of survey data and private and public sector distribution provide some information on the extent of use of spermicides, they are not sufficiently specific to answer all questions. In particular, data are lacking on coital frequency and the use of spermicides, and other characteristics of a typical spermicide users.

Toxicology of Nonoxynol-9

A summary of issues in the toxicological assessment of microbicides, and N-9 in particular, was presented by Ralph Heywood (Consultant Toxicologist, UK). The main challenge for topical microbicides is to balance any irritation, which may be associated with increased risk of lesions and susceptibility to infection, against efficacy. Toxicological assessments allow evaluation of the former. Specifically, it is necessary to determine a dose sufficient to have the desired efficacy while not increasing risk. The balance is further complicated by the fact that the mechanism of action against each outcome (sperm, bacteria, and viruses) differs, as

does the minimally effective dose. All products, even inert devices, cause some degree of epithelial disruption and may alter the vaginal microflora. They thus have the potential to increase penetration by infectious elements. This is particularly an issue for surfactants such as N-9.

A related toxicological concern is clearance: how long the product remains in the vaginal vault after initial application and the effects of retained material. Such issues have not been adequately studied for N-9, which was never tested using current standards of toxicological assessment.

In addition to the specific toxicological questions regarding N-9, there is inadequate information of the safety of the excipients used to formulate the product. This applies to other surfactants as well as to other OTC products, including vaginal and rectal lubricants.

Clinical safety data on Nonoxynol-9

A background paper, which summarised clinical safety data on N-9 had been prepared by Christine Mauck, CONRAD (delivered at the meeting by Marianne Callahan).

Safety data with respect to epithelial disruption were reviewed from a total of 16 studies on four different N-9 formulations: suppository, sponge, gel, and film. The studies differed with respect to their purpose, when they were conducted, the doses and concentrations of N-9 studied, formulation, frequency and duration of use, sample sizes, target populations, comparison products, rules regarding intercourse, and the means of assessing endpoints. Cross-study comparisons were therefore difficult.

Some studies had directly comparable data on frequency of use. Roddy and colleagues compared the effects of different frequencies of use of suppositories each containing 150 mg of N-9.[1] Epithelial disruption was noted in 15% of placebo users, 18% of women who used the product every other day, 34% who used the product daily, 29% who used the product twice per day, and 53% who used the product four times per day.

In a study of sex workers using suppositories containing 100 mg N-9, 28% of users overall showed signs of genital ulcers.[2] In contrast to the earlier Roddy study, there was no evidence of an increased risk of lesions with higher frequency of use. The incidence of cervical lesions was 9.0, 2.2 and 2.7 per 100 woman-months among infrequent users (10 or fewer times per month), intermediate frequency users (11 – 15 times per month) and frequent users (more than 15 times per month), respectively. Comparable figures for vaginal lesions were 3.0, 0.8 and 0.6 per 100 woman-months, respectively.

A study by Van Damme *et al* among sex workers comparing a gel containing 52.5 mg of N-9 with a vehicle gel reported no difference between the two study arms, but that the incidence of genital lesions increased with increasing frequency of use.[3]

Four studies reported on the incidence of epithelial disruption associated with different frequencies of use of vaginal suppositories containing N-9.[1,2,4,5] In general, higher frequency use was associated with higher incidence of disruption (Table 1).

A total of six studies reported on the use of gels containing N-9 with doses ranging from 52.5 mg to 250 mg.[3,6-10] While higher doses appeared to be associated with higher incidence of disruption, there were insufficient data to asses the impact of frequency of use.

With regard to contraceptive film containing 70 mg N-9, there was no clear pattern according to frequency of use. However studies in which women used the product for long periods had higher overall rates of disruption than studies with shorter durations of use.[5,11-13]

The Today® contraceptive sponge contains 1000 mg N-9, but considerably less is bio-available. One study involving 32 women showed no evidence of epithelial disruption,[8] while a second study among a larger group of sex workers showed a higher frequency of lesions in the active compared with the placebo group.[14]

A summary of the evidence regarding the clinical safety of N-9 is given in Table 2. Taken overall, the data from the different products, doses and frequencies of use, showed a trend towards a greater frequency of disruption with greater frequency of use and higher doses of N-9. This trend was most evident in studies of suppositories and the sponge (although data on the sponge are quite limited), where the incidence of epithelial disruption was greater with more frequent use. In general, the literature supports the conclusion that infrequent use of products containing low doses of N-9 is probably safe.

The summary also revealed major obstacles to interpreting the available data on the clinical safety of N-9. In particular, it is unclear what should be considered normal with respect to signs of epithelial disruption and it is not possible to distinguish between epithelial changes resulting from sexual intercourse and the impact of the study product, despite randomised studies in commercial sex workers masked to the exact product used. There is poor correlation between clinical findings and self-reported symptoms, and clinical findings and laboratory markers of inflammation. In addition, the clinical significance of signs and symptoms of disruption is not known, particularly with regard to any increased risk of acquiring an STI or HIV. Furthermore, it is not known how signs and symptoms of disruption correlate with product acceptability and use.

Studies of other surfactants such as benzalkonium chloride[15] and menfegol[16] have shown that these products are also associated with epithelial disruption.

Effectiveness of Nonoxynol-9 for pregnancy prevention

A summary of the available data on the contraceptive effectiveness of N-9 was presented by James Trussell (Princeton University), drawing on the contraceptive efficacy chapter in the latest edition of *Contraceptive Technology* and more recently published studies.[17]

Most studies that have evaluated the contraceptive effectiveness of N-9 were poorly conducted and few were randomized controlled trials. In particular, not all studies had comparison groups, loss to follow-up was often high, and efficacy under conditions of perfect use could not be reliably assessed due to lack of data on consistent and correct use over the full duration of the study. More reliable estimates are available for typical use of the products. In addition, the dose of the product under study, the frequency of product use, and the composition of the target populations (age, level of sexual activity and risk) varied across studies, making comparisons almost impossible.

The typical use pregnancy rates data on spermicides used alone come from 31 clinical trials with exposures ranging from 3 to 67 months, which reported Pearl pregnancy rates, and four clinical trials and six surveys, which reported cumulative 12-month life-table pregnancy rates (Table 31-3 in *Contraceptive Technology*). The typical use pregnancy rates (expressed either as pregnancies per 100 woman-years or as 12-month cumulative life table rates) ranged from

less than 2% in 9 studies, 2% – 5% in four studies, 5% – 10% in eight studies, 10% – 15% in three studies, 15% – 30% in eleven studies, and between 37% and 59% in six studies. Not one of these studies met modern standards of study design, execution, analysis or reporting.

Excluding a recent randomized study (discussed below), the best trial design and analysis was published by Mears and Please in 1962.[18,19] This involved the random assignment to six groups, each of which used three spermicidal products for three cycles each. The six groups represented all permutations of possible orders of use of the three products. Pregnancy rates were reported separately for cycles in which the product was used at every act of intercourse and for cycles where unprotected intercourse occurred. Four pregnancies occurred in 561 cycles of use of Emko vaginal foam (0.71%), which corresponds to a 13-cycle probability of pregnancy of 8.9%. However, this study was marred by a loss to follow-up rate of over 20%, very high considering the short duration of the study.

The only study using modern standards of design, execution and analysis involved 765 women randomly assigned to Vaginal Contraceptive Film (VCF) or Conceptrol foaming tablets.[20] The study subjects were in the age range 18-35 years (58% less than 25 years), had no history suggestive of subfecundity, and had a high coital frequency (71% reported more than 10 acts of intercourse per month). The percentages of women becoming pregnant within 6 months under conditions of typical use were 24.9% (95% confidence interval 20% – 30%) for VCF and 28.0% (23% – 34%) for Conceptrol. The corresponding consistent use pregnancy rates were 24.1% (19% – 30%) and 27.9% (22% – 34%), respectively. The contraceptive efficacy for the two products was similar, but was associated with high rates of pregnancy in this young, sexually active population. It is difficult to interpret these results since there was no comparison group using a method with known efficacy.

The only study to evaluate the ability of Advantage-24 contraceptive gel to inhibit sperm transport and survival involved the application of gel 15 – 30 minutes, 12 hours, and 24 hours before intercourse.[21] The authors concluded that effectiveness may decrease when it is applied more than 15 – 30 minutes before intercourse. However, the postcoital tests were not performed until 8 – 12 hours after intercourse and the results could have been worse if postcoital tests had been performed earlier. In addition, there was no control time or assessment in the study, other than the use of gel applied 15 – 30 minutes before intercourse. Moreover, it is not known how well the postcoital test among normal fertile couples can reflect typical or perfect use pregnancy rates.

Data on pregnancies associated with use of the diaphragm, sponge and cervical cap are more extensive (see Results summarized in Table 31-5, Table 31-6, and Table 31-7 in *Contraceptive Technology*).[17] The typical-use first-year probabilities of pregnancy exceed 8% in most studies with the exception of one study of the diaphragm[22] which showed a first-year probability of pregnancy of 2.1% but had serious methodological errors. Two high quality studies compared the diaphragm to another device. In one, 1439 women were randomly assigned to either the sponge or diaphragm,[23] in the other 1394 women were randomly assigned to the cervical cap or diaphragm.[24] The 12-month typical-use probabilities of pregnancy were 17.2% for the sponge and 12.7% for the diaphragm (first study) and 17.5% for the cervical cap and 16.9% for the diaphragm.[25] These typical-use pregnancy rates correspond to estimated 12-month perfect-use probability of pregnancy in the range 11.4% – 12.0% for the sponge, 4.3% – 6.1% for the diaphragm (first study), and 10.3% – 12.5% for the cervical cap and 5.3% – 8.4% for the diaphragm (second study).[26] In both studies nulliparous women had substantially lower pregnancy rates than parous women when

they used the sponge or cervical cap, but there was no difference according to parity among the diaphragm users.

Two studies have published 12-month probabilities of contraceptive failure during typical use of the diaphragm with and without spermicide. In a study of 110 users of a non-spermicidal fit-free diaphragm the 12 month pregnancy rate was 24.1%.[27] A randomized trial of diaphragm use with or without spermicide showed a typical 12-month pregnancy rate of 21.2% with spermicide and 28.6% without. The corresponding 12-month probabilities of contraceptive failure during consistent use were 12.3% and 19.3%, respectively.[28]

A double-blind study of the Lea's Shield® vaginal contraceptive device used with N-9 spermicide gel or a non-spermicidal comparison gel showed a lower pregnancy rate among the spermicide compared with the control gel (6-month pregnancy rates 5.6 and 9.3, respectively, P = 0.086).[29]

One study of spermicidally-lubricated condoms reported a 2.1% typical-use 12-month probability of pregnancy, but 26% of the men were in the age range 40 – 44 years, 27% in the range 45 – 49 years and 24% were over 50 years. The study subjects had a low coital frequency and their female partners were well beyond the period of peak fecundity. In addition only pregnancies leading to a live birth were reported.[30]

In summary, the data support the conclusion that use of spermicide alone reduces risk of pregnancy compared with use of no product, despite the limitations of the studies. Although spermicides in the USA are mainly used with barrier methods, the increased benefit of such combinations has not been well established. However, existing data do not support any added benefit of male condoms lubricated with N-9 compared with other lubricants. Data quantifying the contraceptive effects of N-9 in various formulations and doses, used with and without barriers, are clearly needed and studies to address this deficit are currently under way.

Effectiveness of Nonoxynol-9 for prevention of sexually transmitted infections

A review of the effectiveness of N-9 for prevention of sexually transmitted infections was given by Ward Cates (Family Health International). This was supplemented with data from two recently completed but not yet published trials presented by the Principal Investigators, Ron Roddy (Family Health International)[31] and Lut Van Damme (Institute of Tropical Medicine, Antwerp, and CONRAD).[32] David Wilkinson (University of South Australia) presented the result of a systematic review of randomized controlled trials.

An in-vitro study assessed the effect of N-9 added to condoms in a model for simulated intercourse. This showed that the added N-9 inside the condoms killed HIV inside the condom before rupture and outside the condom after rupture.[33] However, the extra spermicide ointment was added inside the tip of the condom and it is not clear how these results apply to commercially available condoms lubricated with N-9.

In a randomized, double-blind, placebo-controlled trial comparing 150 mg N-9 gel with placebo among 818 women in Birmingham, Alabama, the risk of first gonorrhoea infection was slightly lower among N-9 than placebo users (RR 0.84, 95% confidence interval 0.60 – 1.17), as was the relative risk for any episode of gonorrhoea infection (RR 0.75, 0.56 – 1.01).[34] Similar results were shown for first Chlamydia infection (RR 0.72, 0.55 – 0.94) and any Chlamydia episode (RR 0.79, 0.62 – 1.01). There were no statistically significant

differences in rates of trichomoniasis (RR 0.83, 0.61 – 1.12), candidiasis (RR 1.02, 0.77 – 1.35) or bacterial vaginosis (RR 0.86, 0.69 – 1.12).[35]

In a study in Bangkok, Thailand, 343 female sex workers who were randomised to 70 mg N-9 film or placebo showed a 25% decrease in the incidence of cervical infection (rate ratio 0.75 [0.5 – 1.1]).[11] The reduction in risk was greater if women reported more consistent condom use.

A study in Nairobi compared use of the Today® contraceptive sponge containing 1000 mg N-9 with a placebo suppository among 138 sex workers.[14] Twenty-one percent of women in the N-9 group developed gonorrhoea compared with 32% in the placebo group (adjusted relative risk 0.4, $p<0.001$). The rates of Chlamydia infection did not differ significantly between study groups (RR 0.6, 2% compared with 4%). Twenty-seven (45%) of 60 women in the N-9 group and 20 (36%) of 56 women in the placebo group developed HIV infection (hazard ratio 1.7 [0.9 – 3.0]).

In a randomized study comparing 70 mg N-9 film with placebo among 1292 female sex workers in Cameroon,[13] the incidence rates of gonorrhoea were 33.3 and 31.1 cases per 100 woman-years in the N-9 and placebo groups, respectively (rate ratio 1.1 [95% confidence interval 0.8 – 1.4]). Corresponding incidence rates of Chlamydia were 20.6 and 22.2 per 100 woman-years in the N-9 and placebo groups, respectively, (rate ratio 0.9 [0.7 – 1.3]). The rates of HIV infection were 6.7 and 6.6 cases per 100 woman-years in the N-9 and placebo groups, respectively (rate ratio 1.0 [0.7 – 1.5]).

A randomized study among 278 female sex workers in Mombassa, Kenya compared an intravaginal gel containing 52.5 mg N-9 with placebo.[10] The incidence rate for gonorrhoea was higher in the N-9 group compared with placebo (RR 1.5 [0.9 – 2.7]), but there were no reported differences in the incidence of Candida, Trichomonas, bacterial vaginosis, Chlamydia trachomatis, syphilis, or HIV.

Ron Roddy reported on a recently completed open-label randomised trial comparing 100 mg N-9 gel plus condoms to condoms alone among 1251 women attending STI clinics in Cameroon.[31] The primary outcome was gonococcal and/or chlamydial infection, with HIV infection as secondary outcome. The incidence of gonococcal infections, chlamydial infections, or both, was 43.6 per 100 person-years in the gel group, and 36.6 per 100 person-years in the condom alone group. The relative risk in the gel group compared with the condom group was 1.5 (1.0 – 2.3) for gonococcal infection and 1.0 (0.7 – 1.4) for chlamydial infection. There were 5 new cases of HIV infection in the gel group and 4 in the condom group.

Lut Van Damme reported on the results from the triple-blind randomized controlled trial comparing a 52.5 mg N-9 gel (COL-1492) with Replens®, an OTC vaginal moisturiser.[32] The study population consisted of 892 sex workers from Benin, Côte d'Ivoire, South Africa and Thailand. There was little effect of N-9 on the incidence of gonococcal (RR 1.2 [0.9 – 1.6]) or chlamydial infection (RR 1.2 [0.8 – 1.6]). However the incidence of HIV infection among N-9 users was 48% higher than among placebo users (14.7 compared with 10.3 cases per 100 woman-years, adjusted relative risk 1.5 [1.0 – 2.2]). For women who reported using more than 3.5 gel applications per working day the risk of HIV infection among COL-1492 users was almost twice (RR 1.8 [1.0 – 3.2]) the risk among placebo users. The risk did not differ between the two treatment arms among women using the gel less frequently. Higher frequency of use of the study products was also associated with a higher incidence of genital

lesions in both study groups, with a greater incidence ratio among N-9 users compared with placebo. These results were dominated by one of the centres which contributed 69% of the HIV seroconversions observed during the study. Considerable discussion at the meeting focused on the validity of self-reported condom use and coital diaries on which the dose-response analyses were based. Potential limitations of the study, such as the low follow-up rate and the use of Replens® as the control product, were also discussed.

The systematic review presented by David Wilkinson confirmed that there was no evidence of any protective effect of N-9 against STIs. Using Cochrane procedures for meta-analysis of randomized trials, data from nine studies including almost 5000 women were included (Table 3). Confidence limits for all outcomes (gonorrhoea, Trichomonas, bacterial vaginosis, and candidiasis) all included 1.0.

The limitations of currently available data were recognized at the meeting. In particular, most of the data on the effectiveness of N-9 in protecting against STIs and HIV come from studies among sex workers or other high risk groups. Few data are available from women who use the product at low frequencies, who are at low risk of infection, or from women who use N-9 alone. In addition it is not known whether adding N-9 to barrier methods such as the cervical cap or the diaphragm has any protective effect against sexually transmitted infections.

Safety of rectal use of Nonoxynol-9

David Phillips (Population Council, New York) presented data on the safety of rectal use of N-9. Rectal application of two N-9 containing products (K-Y Plus and ForPlay®) was evaluated in both a mouse model and human subjects (N = 4); two formulations not containing N-9 (carrageenan and methyl cellulose) were used as controls.[36] In both studies, rectal lavage (saline) revealed significant sloughing of sheets of epithelium. However, no rectal epithelial cells were found in the baseline lavage specimens, any of the lavages involving non-N-9-containing formulations, or, most importantly, in rectal lavage specimens collected 8 hours post N-9 product use, suggesting that any damage had been repaired. Nonetheless, the possibility of increased risk of infection soon after the application of products containing N-9 seems quite likely, even for lubricants not advertised to be microbicidal.

More research is urgently required on the safety of rectal use of N-9 and other lubricants, as well as further understanding of the time course for the rectal damage to repair.

Provider and user perspectives

The regulator's perspective

Helen Rees (University of the Witwatersrand, South Africa and former chair of the South Africa Medicines Control Council) gave an overview of the problems of developing country regulators when faced with the new data on the safety of N-9. OTC product use is particularly problematic with respect to labelling and instructions for use. Products available and effective for one indication, for example contraception, can have unintended adverse effects on other outcomes such as STIs and HIV infections. One solution for products such as N-9 for which may be associated with risk under particular conditions of use, might be to change the OTC status or to specify instructions according to risk. However, because risk involves both individual behaviour (number of sexual partners, frequency of sexual

intercourse, whether or not condoms are used) as well as the local prevalence of infection risk differs for different settings and for different people. Furthermore, recommendations for product use, even as a contraceptive, should depend on the availability of other products, which also varies. As a result, drug approval based on one or two well-conducted studies may not be sufficient for universal guidelines. In fact, guidelines for product use, in this case N-9 containing products, might need to be country-specific. Lack of post-marketing surveillance of OTC products in general, further exacerbates any evaluation of N-9 containing products.

The provider and user's perspective

Joanna Nerquaye-Tetteh (Planned Parenthood, Ghana) provided an overview of the perspectives of providers and users. She stressed the importance of woman-controlled methods of protection from HIV and STIs, as well as the availability of viable contraceptive methods. Guidelines for use of N-9 products need to be considered in their local context, including assessment of the alternative contraceptive options available in a country. In general, with adequate information, women are capable of understanding risks and benefits so that they can make an informed choice, especially with regard to contraception. Women need a variety of contraceptive alternatives, including methods that are convenient to obtain and use and that are effective long-term. The issue of cost and availability of products must also be considered in assessing the contraceptive method mix and availability.

Data were incomplete on the extent of use of N-9 products in different countries, as well as the availability of other products and the ease with which women can switch products.

Conclusions and Recommendations

Conclusions and recommendations for the WHO/CONRAD Technical Consultation on Nonoxynol-9, WHO Geneva, 9 – 10 October 2001

Conclusions

Effectiveness of Nonoxynol-9 for pregnancy prevention

1. Nonoxynol-9 (N-9) when used alone is moderately effective as a contraceptive.

2. For women who choose to use N-9 alone in preference to other methods, it is better than no contraceptive method at all.

3. When used with a female mechanical barrier method (for example a cervical cap or diaphragm) N-9 is more effective than when used alone.

4. N-9 is available in a number of different formulations (film, sponge, gel, suppository, and foam) and doses. It is not known whether contraceptive effectiveness differs according to formulation or dose.

5. There is no evidence that condoms lubricated with N-9 are more effective in preventing pregnancy than lubricated condoms without N-9.

6. Limited evidence suggests that the contraceptive effectiveness of the diaphragm and cervical cap may be moderately more effective when used with a spermicide than without.

Safety of Nonoxynol-9

1. N-9 is a surfactant which disrupts the cell membrane. It has been shown to be an irritant in animal as well as human models.

2. N-9 has been shown to cause epithelial disruption in the vagina and rectum.

3. Increasing frequency of use of N-9 suppositories increases the risk of vaginal epithelial disruption. No other studies designed to look specifically at the effect of frequency of use with other formulations of N-9 have been published. However observational studies have shown increased rates of epithelial disruption with greater frequency of use of N-9.

Effectiveness of Nonoxynol-9 for prevention of sexually transmitted infections including HIV

1. There is good evidence that N-9 does not reduce the risk of sexually transmitted infections (STIs) or HIV among sex workers nor women attending STI clinics.

2. Most of the clinical evidence on the risk of HIV infection with use of N-9 comes from studies conducted among women who were sex workers or women attending STI clinics.

3. No studies on the effectiveness of N-9 to prevent infection with STI or HIV have been conducted in other groups of women.

Recommendations

These recommendations are based on the above evidence and on consideration of the balance of risks and benefits to individual users. Family planning programmes in different countries and communities must consider these recommendations in the light of their particular circumstances, including the prevalence of HIV and sexually transmitted infections, and the range of available contraceptive options.

Nonoxynol-9 for STI prevention

N-9 should not be used for the purpose of STI or HIV prevention. Condoms should always be used to prevent infection.

Nonoxynol-9 for contraception

Among women at low risk of HIV infection, the use of N-9 remains a contraceptive option. Although its effectiveness is low compared with other contraceptive methods, it is generally easily available, can be obtained OTC without requiring a medical consultation or prescription, and is a method under the control of the woman.

1. Since high frequency use of N-9 products may cause epithelial damage and increase the risk of HIV infection, women who have multiple daily acts of intercourse should be advised to choose another method of contraception.

2. Women at high risk of HIV infection should not use N-9 for contraception, since N-9 may increase the risk of infection.

Rectal use of Nonoxynol-9

N-9 should not be used rectally.

Use of Nonoxynol-9-lubricated condoms

There is no published scientific evidence that N-9-lubricated condoms provide any additional protection against pregnancy or STIs compared with condoms lubricated with other products. Since adverse effects due to the addition of N-9 to condoms cannot be excluded, such condoms should no longer be promoted. However, it is better to use N-9-lubricated condoms than no condoms.

Key areas of uncertainty and the need for further research

1. The safety concern about N-9 may also apply to other spermicide products marketed for contraception. Their safety should be formally assessed as a matter of urgency. This also applies to vaginal or rectal lubricants which contain N-9.

2. The safety of lubricants containing only ingredients thought to be inactive which are used vaginally and/or rectally needs to be assessed as a matter of urgency.

3. There is an urgent need to develop safe lubricants for rectal use.

4. The precise clinical significance of epithelial disruption observed in safety studies is not known.

5. There are currently no published studies on the effect of N-9 among women with HIV infection.

6. Continued work is urgently required to develop safe and effective microbicides.

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Table 1: Incidence of epithelial disruption according to frequency of use of suppositories containing N-9

Study	N	Risk	Dose (mg)	Freq.	Duration	Disruption active	Disruption placebo
Roddy[1]	34	Low	150	QID	14 days	53%	15%
Niruthisard[4]	15	Low	150	QID	14 days	43%	0%
Roddy[1]	34	Low	150	BID	14 days	29%	15%
Roddy[1]	35	Low	150	QD	14 days	34%	15%
Coggins[5]	145	Low	150	≤QD	4 weeks	0% in all	NA
Roddy[1]	34	Low	150	QOD	14 days	18%	15%
Weir[2]	191	High	100	QOD	1 year	28% ulcers	NA

NA: Not applicable

Table 2: Summary of clinical safety of N-9 according to formulation.

	Suppository	Gel	Film	Sponge
Number of studies	4	6	4	2
Overall disruption	High in most studies	Low – moderate	Low – high	Low – moderate
Effect of frequency of use	Stepped increase in disruption with increased frequency	Cannot evaluate	No pattern	Increased frequency may increase disruption
Effect of dose	Cannot evaluate	Increased dose may increase disruption	Cannot evaluate	Cannot evaluate
Effect of duration	No pattern	No effect	Increased duration may increase disruption	Increased duration may increase disruption
Effect of study population	No pattern	No pattern	No pattern	More disruption may be seen in high-risk populations
Compared with placebo	Worse	About the same	About the same	Worse

Table 3: Meta-analysis of studies assessing the impact of N-9 on the risk of sexually transmitted infections – relative risk for N-9 compared with placebo (from Wilkinson).

Outcome	Number of studies	Number of participants	Relative risk (95% confidence interval)	
Gonorrhoea	6	3017	0.97	(0.85 – 1.11)
Chlamydia	5	2955	0.88	(0.77 – 1.01)
Cervical infection	2	1584	1.01	(0.84 – 1.22)
Trichomoniasis	3	1101	0.84	(0.69 – 1.02)
Bacterial vaginosis	1	770	0.88	(0.74 – 1.04)
Candidiasis	3	1360	0.97	(0.84 – 1.12)
HIV	5	3570	1.14	(0.92 – 1.41)

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